Corticosteroids in idiopathic pulmonary fibrosis

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Corticosteroids were the mainstay of therapy for idiopathic pulmonary fibrosis (IPF) for more than four decades, but their efficacy is unproven and toxicities are substantial. The course of IPF is characterized by progressive respiratory insufficiency, leading to death within 3 to 8 years from the onset of symptoms. Although a subset (10–20%) of patients survives more than 10 years, there is no evidence that any form of therapy alters the natural history of the disease. Nonetheless, given the poor prognosis, a trial of corticosteroids is often given. Because of the rarity of IPF, randomized, placebo-controlled therapeutic trials have not been done. Further, no studies have compared differing dosages or duration of corticosteroid in matched patients. Interpretation of therapy efficacy is obscured by several factors including heterogeneous patient populations, inclusion of patients with histologic entities other than usual interstitial pneumonia, lack of objective, validated endpoints, different criteria for "response." We review published data regarding corticosteroid therapy for IPF and present a rationale for stratifying therapy based on host, demographic, and clinical factors that influence prognosis as well as risk for corticosteroid complications. Curr Opin Pulm Med 2001, 7:298–308

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Abbreviations

AZA	azathioprine
CFA	cryptogenic fibrosing alveolitis
CS	corticosteroids
DIP	desquamative interstitial pneumonia
ECM	extracellular matrix
GGO	ground glass opacities
HRCT	high-resolution computed tomography
IIP	idiopathic interstitial pneumonias
IPF	idiopathic pulmonary fibrosis
NSIP	nonspecific interstitial pneumonia
PFT	pulmonary function test
RBILD	respiratory bronchiolitis interstitial lung disease
UIP	usual interstitial pneumonia

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Corticosteroids (CS) have been the mainstay of therapy for idiopathic pulmonary fibrosis (IPF) for more than four decades [1–3], but their efficacy is unproven [4••,5–7] and toxicities are substantial [4••,8••]. The terms IPF and cryptogenic fibrosing alveolitis (CFA) are synonymous [3,9,10]. A recent international consensus statement concluded "usual interstitial pneumonia (UIP) is the histopathologic pattern that identifies patients with IPF" [3]. Other histologic patterns have a better prognosis and higher rate of response to CS than UIP and are considered distinct entities [3]. Cardinal features of IPF/CFA include dry cough, exertional dyspnea, end-inspiratory Velcro rales, diffuse parenchymal infiltrates on chest radiographs, honeycomb cysts, a restrictive defect on pulmonary function tests (PFT), impaired gas exchange, and impaired oxygenation (Table 1) [3,10–12]. The course is indolent but inexorable with progressive respiratory failure [13]. Fewer than 40% survive 5 years; the mean survival is 2.8 to 3.6 years [4••,5,7,14–17]. Because IPF/CFA is rare (estimated prevalence rates of three to 20 cases per 100,000 population) [3,12,18,19], randomized, placebo-controlled therapeutic trials have not been done. CS are most often used, but dose, rate of taper, and duration differ among studies [1,2,10,20–22]. Interpretation of published data is misleading because patients with histologic entities other than UIP (and that have a better prognosis than UIP) were included in earlier reports of IPF/CFA.

Definition of idiopathic pulmonary fibrosis

Historically, the histologic lesion UIP was considered to represent a subset of patients with IPF [23,24]. Current recommendations restrict the term IPF to patients with idiopathic UIP [3]. Other types of idiopathic interstitial pneumonia (IIP) include desquamative interstitial pneumonia (DIP) [24,25], respiratory bronchiolitis interstitial lung disease (RBILD) [25], nonspecific interstitial pneumonia/fibrosis (NSIP) [14,15,17,26,27], acute interstitial pneumonia [28,29], lymphoid interstitial pneumonia [30], and cryptogenic organizing pneumonia, also termed bronchiolitis obliterans organizing pneumonia [31]. These types of IIP have a better prognosis and higher rates of response to CS compared with UIP. A definitive diagnosis of UIP requires surgical (open or video-assisted thoracoscopic lung biopsy) [3,25], but the diagnosis of UIP can be confirmed with confidence by thin-section high-resolution computed tomography (HRCT) scans in some patients [27,32]. Most published series of IPF or CFA likely incorporated a mixture of histologic entities [1,2,20–23,33,34]; it is plausible that most steroid-responsive cases of IPF represented disor-

Table 1. Characteristic features of usual interstitial pneumonia

Category	Features
Clinical	Dry cough, exertional dyspnea
Physical exam	End-inspiratory rales, clubbing
High-resolution CT	Patchy involvement, course reticular/linear opacities, honeycomb cysts, basilar/subpleural involvement, traction bronchiectasis
Pulmonary function	Reduced lung volume, reduced diffusing capacity for carbon monoxide, hypoxemia, increased alveolar-arterial oxygen difference
Histopathologic	Heterogeneous distribution, fibroblastic foci, excessive collagen and extracellular matrix, honeycomb cysts

ders other than UIP. When the diagnosis of UIP is substantiated, response to therapy is poor and mortality is high [14,15,17,27].

Histopathologic features of usual interstitial pneumonia

The cardinal histopathologic features of UIP include bilateral but heterogeneous (patchy) involvement, a predilection for the lower lobes and peripheral (subpleural) regions, fibroblastic foci (aggregates of proliferating fibroblasts and myofibroblasts), excessive collagen and extracellular matrix (ECM), and honeycomb cysts [3,25]. Mononuclear cell infiltrates (*eg,* lymphocytes, plasma cells, macrophages) and scattered neutrophils and eosinophils may be present within alveolar septa, but inflammatory changes are not conspicuous [25]. The heterogeneity of the histologic lesion can be seen at low-power magnification; areas of normal lung interstitial inflammation, fibrosis, and honeycomb cysts are observed concomitantly [3,25]. Additional features of UIP include traction bronchiectasis and bronchiolectasis, reduced airspace volume, destroyed or distorted alveolar architecture, smooth muscle hypertrophy, reactive metaplasia and hyperplasia of type II pneumocytes, mucostasis, and secondary pulmonary hypertensive changes [17,25].

Which histologic features differentiate usual interstitial pneumonia from other idiopathic interstitial pneumonias?

Temporal heterogeneity is the central feature that distinguishes UIP from other types of IIP [14,15,17,25]. Fibroblastic foci and honeycomb cysts are prominent features of UIP but are absent or inconspicuous in other types of IIP [25]. Inflammatory cells are not prominent in UIP in contrast to cellular NSIP, DIP, or hypersensitivity pneumonia [25]. Despite the gold standard status of open lung biopsies [25], evaluation is subject to interobserver and intralobar variation, even by expert pulmonary pathologists [35••,36]. Discriminating UIP from fibrotic NSIP is difficult [35••,36]. Further, surgical lung biopsy is expensive and carries significant morbidity and even mortality [37,38]. In clinical practice, open (or video-assisted thoracoscopic surgical) biopsies are performed in only 10 to 30% of patients with IPF [7,11,12]. Since the advent of HRCT scans, many clinicians rely on them to corroborate the diagnosis of UIP [3,4••,27,39].

High-resolution computed tomography

High-resolution CT scans, using 1- to 2-mm thin sections, are often used in lieu of surgical lung biopsies to diagnose UIP [3,14,27,40,41]. Provided HRCT features are classical, the accuracy of a confident diagnosis of UIP on HRCT by a trained observer is greater than 90% [3,42,43]. However, a confident diagnosis of UIP can be made in less than two thirds of patients with histologic UIP [3,43]. Inter- and intraobserver variability can be problematic for inexperienced radiologists, particularly in less severe cases [44].

What are the salient high-resolution computed tomography features that allow a confident diagnosis of usual interstitial pneumonia?

Characteristic HRCT features of UIP include a distinct predilection for the basilar and peripheral (subpleural) regions of the lungs, patchy involvement, large areas of spared lung parenchyma, coarse reticular or linear opacities (intralobular and interlobular septal lines), honeycomb cysts, and traction bronchiectasis or bronchiolectasis [15,27,39,45,46]. Focal areas of ground glass opacities (GGO) are sometimes present in UIP [15,45,47,48], but extensive areas of GGO suggest an alternative diagnosis (*eg,* DIP, NSIP, hypersensitivity pneumonia) [3]. Honeycomb cysts are a cardinal feature of UIP [15,34, 39,45,47] but are rare in other types of IIP [15,25,27].

How reliable is high-resolution computed tomography in assessing prognosis or responsiveness to therapy?

The extent and pattern of changes on HRCT are invaluable in assessing prognosis and responsiveness to therapy [27,34,45,46,49–51]. GGO may reflect alveolar inflammation, intraalveolar granulation tissue, or fibrosis of intralobular and alveolar septa [39,45,46,52]. A reticular pattern reflects fibrosis, but inflammation may coexist [39,45,51,53]. Honeycomb cysts indicate irreversible destruction of alveolar walls and fibrosis [34,45,48,49,53–55]. A pattern of predominant GGO on HRCT predicts a higher likelihood of response to CS therapy and improved survival compared with reticular or honeycomb patterns [34,46,50,51,55–57]. After CS therapy, GGO regress in 30 to 44% of patients [34,39,55]; however, GGO may progress to irregular reticular opacities or honeycomb cysts [34,39,51,53]. Reticular patterns or honeycomb cysts never improve and may worsen over time [34,39,45,53,55]. Most patients with IPF display mixed patterns [34,55]. In published series of IPF/CFA, approximately 10% of patients had predominantly GGO on

HRCT [34,55], but surgical lung biopsies were not performed in many patients. It is likely that patients with predominant GGO had diseases other than UIP (*eg*, DIP, NSIP, hypersensitivity pneumonia). Further, the long-term impact of CS on altering the natural history of IPF/CFA is not known. Japanese investigators retrospectively reviewed serial CT scans of 29 patients with IPF (17 were treated with CS) [53]. Although GGO initially decreased with therapy, progression to honeycomb cysts ensued in 90% of patients.

Extensive fibrosis (reticulation or honeycomb cysts) on HRCT is a poor prognostic sign. Gay *et al*. [49] prospectively studied 38 patients with IPF to identify pretreatment variables that could predict response to CS therapy and long-term survival. Open or video-assisted thoracoscopic surgical lung biopsies and CT scans were quantitatively scored. Pretreatment CT alveolar (CT-alv) and fibrotic (CT-fib) scores predicted responsiveness to therapy and mortality. Responders to prednisone therapy had higher CT-alv scores and lower CT-fib scores compared with nonresponders or the stable group. Survivors had higher CT-alv and lower CT-fib scores compared with those who died during follow-up. Severe fibrosis on pretherapy HRCT (CT fibrosis score ≥ 2) predicted mortality with 80% sensitivity and 85% specificity [49]. HRCT was a better predictor of survival than pulmonary function tests (PFT), clinical/radiographic/physiologic scores, or pathologic scores (from surgical lung biopsies).

Pathogenesis of usual interstitial pneumonia

The pathogenesis of UIP is unclear, but epithelial cell injury, destruction of subepithelial basement membrane, recruitment and proliferation of fibroblasts, and excessive deposition of extracellular matrix (ECM) and collagen are pivotal in orchestrating the fibrotic process [58••]. Early hypotheses emphasized sustained alveolar inflammation [59,60] as a precursor to fibrosis. Activated alveolar macrophages, lymphocytes, and neutrophils were considered the immune effector cells driving the inflammatory process [59], leading to repetitive lung injury and fibrosis [61]. However, there is little evidence to support this hypothesis, and the relevance of chronic inflammation to the development of fibrosis is not clear [62]. Recent studies underscore the importance of fibroblasts, myofibroblasts, abnormal ECM deposition, and myriad cytokines and soluble factors in the pathogenesis of UIP [58••].

Injury of alveolar epithelial cells and destruction of subepithelial basement membranes appear to be key events in the pathogenesis of UIP [62,63]. After lung injury, fibroblasts migrate and proliferate into the alveolar septa and spaces [62,64]. Areas of rapidly proliferating myofibroblasts and fibroblasts (fibroblastic foci) [65] are the primary sites of ongoing injury and repair, leading to collagen deposition [62]. Transforming growth factor β1 stimulates fibroblast proliferation and differentiation into myofibroblasts, stimulates synthesis of collagen and ECM proteins, inhibits synthesis of proteases that degrade the ECM, and likely plays a pivotal role in orchestrating fibrogenesis in UIP [62,66]. Fibroblasts and myofibroblasts from patients with UIP induce apoptosis and necrosis of alveolar epithelial cells *in vitro* [62,67]. Alveolar epithelial shedding, in turn, releases transforming growth factor β1 from ECM, which promotes myofibroblast production of collagen [68]. Fibroblasts from patients with UIP demonstrate enhanced production of collagens [58••], increased expression of tissue inhibitors of metalloproteinases, and a relative decrease in collagenases [62,69]; all these processes promote the formation of scar.

Alveolar macrophages elaborate profibrotic cytokines (*eg*, platelet-derived growth factor [70], insulin-like growth factor I [71], interleukin-1 [72]), ECM proteins [70], and free oxygen radicals [73], which may be important in the pathogenesis of UIP.

Production, deposition, and proteolysis of ECM are critical to pulmonary remodeling, repair, and development of fibrosis. ECM proteins (*eg*, tenascin [65,74], fibronectin [58••], collagen [75]) are expressed in increased amounts in UIP. In the initial phases, both type III and I collagen accumulate; later, type I predominates [75]. Type I collagen reflects irreversible fibrosis attributable to greater resistance to metalloproteinase digestion [62]. Tenascin, another ECM protein, is present in increased amounts in UIP [65] and may correlate inversely with survival [74]. Another ECM protein, fibronectin may be important in the pathogenesis of UIP. Fibronectin acts as a growth factor and chemoattractant for fibroblasts [62,76]. In one study, alveolar macrophages from patients with UIP produced fibronectin at a rate 20 times higher than normal alveolar macrophages [77]; this may promote local recruitment of fibroblasts and collagen deposition, promoting local fibrosis.

Angiogenesis and the production of angiogenic factors by host cells likely contribute to the pathogenesis of UIP. Neovascularization may promote fibrogenesis [62], perhaps by supplying blood to rapidly proliferating fibroblasts within fibroblastic foci. Chemokines (chemotactic cytokines) may promote fibrosis in patients with IPF [78]. Other angiogenic molecules, such as vascular endothelial growth factor and acidic and basic fibroblast growth factor may be involved in the pathogenesis of UIP, but data are lacking [78].

Other molecules believed to play some role in the pathogenesis of UIP include interleukin-1 receptor antagonist

[79], integrin-mediated adhesion molecules [80], surfactant proteins [81], and oxidants [82]. In summary, alveolitis and chronic inflammation likely play roles in the pathogenesis of UIP, but their importance is probably minor [62]. The most critical factors orchestrating the fibrotic process are altered fibroblast phenotype and interactions between immune and nonimmune cells, which lead to profibrotic cytokines. Elucidating the mechanisms of fibrosis in UIP will facilitate the development of novel, targeted therapies for this devastating disease.

Therapy of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis is a frustrating disease to treat because the disease progresses inexorably in most patients, regardless of therapy [13]. Historically, CS or immunosuppressive or cytotoxic agents were used to treat IPF in an attempt to ablate any inflammatory component. However, large retrospective studies found no survival benefit with any form of therapy [3,4••,5,6]. Despite the lack of proven efficacy, CS therapy is offered in 39 to 66% of patients with IPF; treatment is often withheld in the elderly because of concern about adverse effects [4••,5–7,11]. In one clinical survey, 61% of IPF patients younger than age 70 were treated with CS compared with only 28% of patients older than age 70 [7]. Immunosuppressive or cytotoxic agents were used in only 2 to 17% of patients (primarily in patients failing or experiencing adverse effects from CS [4••,5,7,11]. Anecdotal responses were cited with cytotoxic agents (*eg,* azathioprine [AZA], cyclophosphamide)[2,20–22,33,83], but the efficacy of these agents is unproven [4••,5,6,21,84,85]. Similarly, colchicine [4••,86] and D-penicillamine [87] have been used to treat IPF/CFA but are of unproven benefit. In 1995, Hunninghake and Kalica [88], summarizing a working conference on IPF convened by the National Heart, Lung, and Blood Institute (NHLBI) in 1994 noted that "there was a general consensus at the workshop that pulmonary fibrosis is a highly lethal lung disorder and that current therapies for this disease have little effect on the natural history of the disease." In 1999, a summary of a 1998 NIHLBI workshop on IPF arrived at a similar conclusion: "…these observations suggest that current therapy has minimal or no beneficial effect for patients with IPF" [89]. More recently, a recent International Consensus Statement concluded "no data exist that adequately document any of the current treatment approaches improves survival or the quality of life for patients with IPF" [3]. These conclusions are sobering and suggest that novel therapies are essential to improve the prognosis of this fatal disorder [88,89]. In this review, we focus on the role (if any) of CS to treat IPF/CFA. A discussion of other potential therapies for IPF/CFA is beyond the scope of this paper and is addressed only briefly.

Impact of corticosteroids in idiopathic pulmonary fibrosis: results of retrospective studies

The largest series of UIP comprised 487 patients seen at the Mayo Clinic from 1994 to 1996 [4••]. The diagnosis of UIP was confirmed by open lung biopsies in 20% and by HRCT in 80%. Median survival was 3.2 years from the time of diagnosis. Efficacy of therapy was evaluated retrospectively by a review of clinical records. Treatment regimens included prednisone alone in 54, colchicine plus prednisone in 71, colchicine alone in 167, other treatment in 38, and no therapy in 154. By univariate analysis, the use of prednisone or prednisone plus colchicine was associated with a worse survival compared with no therapy. On multivariate analysis, older age, male gender, lower diffusing capacity for carbon monoxide (DLCO), and a history of worsening lung function were associated with worse survival. When these factors were taken into account, survival among patients receiving prednisone was similar to untreated patients. Another retrospective study of 244 patients with CFA cited higher mortality rates among patients treated with either CS or cyclophosphamide [5]. Mean survival was 3.6 years for prevalent cases and 2.3 years for incident cases. CS were used in 47% of 76 incidence cases and 65% of 168 prevalent cases. Odds ratio (OR) for mortality was worse among prednisone-treated patients, both in the incident cohort (OR: 2.01) and prevalence cohort (OR: 2.08). The worse survival among patients treated with CS likely reflects selection bias because sicker patients were probably treated more aggressively. A prospective survey from 1991 to 1992 in England, Scotland, and Wales identified 588 patients with a new diagnosis of CFA [12]. Open lung biopsies were done in only 12.4%. No treatment was offered in 48%; the remaining patients were treated with CS and immunosuppressive or cytotoxic drugs. By October 1994, 45% of patients had died; the impact of treatment was not determined. A retrospective review of 234 patients with UIP (confirmed by open lung biopsies or autopsies) from Japanese hospitals cited similar mortality rates among untreated patients compared with patients treated with CS [6].

Several early studies of patients with IPF/CFA cited response rates of 10 to 30% with CS (alone or combined with immunosuppressive agents) [1,2,20–22,33,83,84], but complete or sustained remissions were rare. Two studies in the mid-1980s cited beneficial responses to high-dose CS in patients with IPF/CFA with lymphocytosis on bronchoalveolar lavage [22,33]. These various published series of IPF or CFA failed to classify patients according to histologic entities (*eg,* UIP, DIP, NSIP) and cannot be extrapolated to UIP. It is plausible that steroid-responsive patients had cellular NSIP (or some other IIP) and not UIP. Retrospective reviews of open lung biopsies previously labeled as IPF or CFA revealed

that only 47 to 71% of cases were UIP, 13 to 36% were reclassified as NSIP, and the remaining patients were categorized as DIP, RBILD, or miscellaneous [14,15,17, 27,35••,36]. Compared with other types of IIP, UIP exhibits considerably lower survival rates and responsiveness to therapy [14,15,17,27,35].

What is the response to corticosteroids among idiopathic pulmonary fibrosis patients in prospective randomized trials?

A few randomized therapeutic trials compared CS with immunosuppressive or cytotoxic agents [20,21,23,90] or colchicine [40] as therapy for IPF. These studies did not subclassify patients as UIP. One 6-month study at the National Institutes of Health randomized 28 patients with mid-course IPF to prednisone alone (n = 16), prednisone plus oral CP (n = 9), or CP alone (n = 5) [90]. At 6 months, PFT or chest radiographs did not change in any group. Another prospective trial in England randomized 43 patients with untreated IPF to high-dose prednisolone alone (60 mg/d with gradual taper) or oral CP plus low-dose prednisolone (20 mg every other day) [21]. Symptoms, chest radiographs, and PFT were monitored as endpoints. Seven of 22 patients (31%) receiving prednisolone alone showed initial improvement. At 3 years, only two patients treated with prednisolone alone maintained improvement, and 15 had worsened (10 deaths). Two prospective studies evaluated high-dose prednisolone plus AZA for IPF [20,23]. In the first study, 20 patients with progressive IPF were treated with high-dose prednisone alone for 3 months [23]. At 3 months, AZA, 3 mg/kg/d, was added, and both agents were continued for an additional 9 months or longer. Overall, 12 patients (60%) improved (defined as increase in vital capacity $\geq$ 20% above baseline) but the concomitant use of AZA obscures the effect of prednisone. In a second, double-blind trial by these investigators, 27 patients with newly diagnosed IPF were randomized to receive AZA plus high-dose prednisone, 1.5 mg/kg/d, with taper (n = 14) or high-dose prednisone plus placebo (n = 13) [20]. At 1 year, four patients died in each group. Changes in PFT were minimal and were similar between groups. At 1 year, vital capacity improved (>10% above baseline) in three of 13 patients receiving prednisone alone; DLCO improved (> 20% above baseline) in only two patients. At long-term follow-up (at a mean of 9 years), 77% in the prednisone plus placebo cohort had died (compared with 43% of AZA-treated patients). This survival difference was not statistically significant ($P = 0.16$). Investigators at the Mayo Clinic randomized 26 patients with idiopathic UIP to colchicine (0.6 mg once or twice daily) (n = 14) or high-dose prednisone (n = 12) [40]. PFT did not improve in any subject in either group. Side effects were more frequent and severe in the prednisone cohort. A prospective but nonrandomized study from Mexico evaluated four patient cohorts with IPF [87]. Treatment regimens included colchicine plus prednisone (n = 19); D-penicillamine plus prednisone (n = 11); prednisone plus colchicine plus D-penicillamine (n = 11) or prednisone alone (n = 15). Five-year mortality was 52% and did not differ between treatment groups [87]. We recently published our experience of 41 patients with IPF treated with high-dose CS (1 mg/kg/d, with taper) [8••]. Eleven patients (27%) improved (defined by $\geq$ 10-point drop in clinical/radiographic/physiologic scores); 19 (46%) remained stable; 11 (27%) deteriorated. Survival was improved among patients who remained stable or responded to therapy compared with nonresponders. However, additional factors independently affected survival (*eg,* extent of fibrosis on CT or lung biopsy). Importantly, on review of open lung biopsies (initially diagnosed as UIP), most steroid-responsive patients had NSIP and not UIP.

What is the response to corticosteroids among patients with a histologic diagnosis of usual interstitial pneumonia?

When the diagnosis of UIP is confirmed by surgical lung biopsies, survival and response rates (to any form of therapy) are dismal (0–16%) [14,15,24,27,35••,45,54,91]. Most data are gleaned from retrospective studies. A retrospective review of open lung biopsies at the Mayo Clinic from 1976 to 1985 identified 63 patients with UIP [14]. Although data regarding therapy were not provided, 89% were treated with CS. Median survival (entire cohort) was 2.8 years; only 20% survived 5 years. Another study from the Mayo Clinic retrospectively compared 22 patients with UIP treated with prednisone alone with 22 patients with UIP treated with colchicine alone [86]. Vital capacity improved to more than 15% above baseline in only one of 22 receiving prednisone. Japanese investigators cited a 7-year survival rate of 23% among 64 patients with UIP [15]. None of 30 patients treated with CS improved [15]. In a recent retrospective British study [27], 13 patients with UIP were treated with CS or immunosuppressive agents (alone or in combination). Only one improved (7%); the mean survival was 2.7 years. In another retrospective study, these investigators analyzed 37 patients with UIP (confirmed by open lung biopsies) [35••]. Twenty-eight patients were treated with CS (alone or with immunosuppressive agents); only three (11%) responded. At 42 months, only four patients (11%) were alive [35••]. A retrospective review of open lung biopsies from the National Institutes of Health detected 56 cases of UIP [17]. Five- and 10-year survival rates for UIP were 43 and 15%, respectively. Data regarding therapy were not provided. These data suggest that earlier studies of IPF/CFA citing response rates of as high as 30% likely included a mix of histologic lesions other than UIP.

*Steroid responders may represent histologic subsets other than usual interstitial pneumonia (*eg, *nonspecific interstitial pneumonia, desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease, chronic hypersensitivity pneumonia)*

In contrast to the dismal response rates to CS observed with UIP, steroid responsiveness and survival are substantially better among patients with other types of IIP (*eg*, NSIP [14,15,27,35••,91] or DIP/RBILD [14,17,24,25,92]. Prognosis of DIP/RBILD is generally excellent (with or without CS therapy), with survival rates as high as 90% at 10 years [14,17,24,25]. The prognosis of NSIP is less well established, but retrospective studies cite 5- and 10-year survival rates exceeding 70% in some series [14,15,27,35••,91]. Further, a significant proportion (45–83%) with cellular NSIP respond to CS therapy [15,25,93,94]; the prognosis for fibrotic NSIP is worse (response rates to CS as low as 30%; < 50% 5-year survival) [35••]. Previous reports of steroid-responsive IPF/CFA correlating with GGO on HRCT [34,46,50,51, 55–57] or bronchoalveolar lavage lymphocytosis [22,33] may reflect inclusion of histologic entities other than UIP (*eg*, NSIP, RBILD, chronic hypersensitivity pneumonia). Although data are limited, we believe CS are warranted for NSIP or cases of DIP/RBILD with persistent symptoms or pulmonary dysfunction despite cessation of cigarette smoking [92].

Complications of corticosteroid therapy

Corticosteroid therapy is associated with myriad adverse effects that are related to both the dose and duration of treatment [95,96]. Side effects of CS can be debilitating and include musculoskeletal complications (vertebral compression fractions, aseptic necrosis of femoral and humeral heads, osteoporosis, myopathy), neuropsychiatric effects (psychosis, depression, irritability; insomnia, inappropriate euphorias), endocrine and metabolic alterations (hyperglycemia, metabolic alkalosis, salt and water retention), opportunistic infections, weight gain, truncal obesity, Cushingoid features, peptic ulcer disease, exacerbation of hypertension, posterior capsular cataracts; menstrual irregularities. The use of CS to treat any disease requires a careful assessment of potential risks and potential benefits associated with therapy. This certainly applies to IPF/UIP, where the efficacy of CS therapy is unproven. The risk of CS therapy may outweigh the benefit in populations at increased risk of CS adverse effects (*eg*, age > 70 years, extreme obesity, osteoporosis, diabetes mellitus, underlying psychiatric disorder). CS effects may be devastating in the elderly [7,8••,40].

A recent study of 374 patients receiving oral CS for various lung diseases cited a significant increased rate of complications compared with control subjects not receiving CS [95]. There was a higher incidence of fractures, muscle weakness, back pain, bruising, oral candidiasis, use of histamine-2 antagonists, and cataracts among CS-treated patients. The effects of CS were dose dependent. The frequency of CS-associated adverse effects is high among patients with IPF, many of whom are elderly or have comorbidities [8••,40,97]. When questionnaires were done prospectively to assess CS effects among patients with IPF, adverse effects were nearly invariably observed [8••,40]. Douglas *et al.* [40] prospectively analyzed side effects among 12 IPF patients treated with high-dose CS. The most commonly reported side effects included Cushingoid features (75%), diabetes mellitus (50%), insomnia (50%), myopathy (42%), muscle cramps (42%), depression (25%), and epigastric pain (25%). Similarly, we prospectively evaluated 41 IPF patients treated with a 3-month course of high-dose CS [8]. All 41 patients experienced at least one complication of CS during the first 3 months of treatment. The frequency of these complications is shown in Table 2. Although CS benefits some patients, the high incidence of adverse effects underscores the need to stratify risk for CS complications when treatment is being contemplated. In the following sections, we discuss ways to minimize the risk of CS adverse effects.

Osteoporosis

Osteoporosis is a well-recognized complication of CS and can lead to fractures [98]. Potential mechanisms by which CS lead to bone loss and osteoporosis include decreased production of testosterone, decreased calcium absorption, increased calcium excretion, and decreased

Table 2. Selected side effects during 3 months of high-dose steroid therapy in 41 patients with idiopathic pulmonary fibrosis

Category	Patients, *n* (%)
Psychological	
Irritability	25 (61)
Insomnia	31 (76)
Depression	15 (37)
Musculoskeletal	
Spontaneous fracture	2 (5)
Avascular necrosis	2 (5)
Infection	
Local	11 (27)
Systemic	9 (22)
Gastrointestinal	
Abdominal bloating	14 (34)
Peptic ulcer	1 (2)
Endocrine/metabolism	
Glucose impairment	10 (24)
Hypertension	3 (7)
Weight gain	29 (71)
Edema	17 (41)
Muscle cramping	15 (37)
Fatigue	12 (32)
Dermatologic	
Cushingoid change	30 (73)
Acne	11 (27)
Easy bruising (echymosis)	13 (32)

All patients experienced at least one side effect. Adapted with permission [8].

production of osteocalcin by osteoblasts [99]. Simple nonpharmacologic measures advocated to reduce bone loss include (1) increasing activity, (2) maintaining good nutrition, (3) refraining from smoking, and (4) modulating consumption of alcohol [99]. Supplemental calcium and vitamin D are recommended for patients receiving CS, but this strategy does not consistently prevent osteoporosis in high-risk patients. The risk of fractures is increased considerably among patients receiving high-dose CS. In a recent study, the risk of hip fracture over 4 years was doubled in patients taking oral CS compared with that of controls [100]. In another study of 367 patients taking CS for diverse lung diseases, the cumulative incidence of fractures (all sites) was 23% for patients receiving oral CS compared with 15% in controls not receiving CS (OR: 1.8) [95]. More important, among CS-treated patients, the risk of fractures was markedly increased (compared with controls) at the following sites: vertebrae (OR: 10), hips (OR: 6), and ribs or sternum (OR: 3.2).

Measurement of bone mineral density (BMD) is recommended as a proxy measure of bone strength and to assess the risk of fracture [98]. Baseline BMD should be measured in patients receiving long-term CS treatment, particular in the elderly or postmenopausal women [98]. Pharmacologic therapy should be considered for patients with BMD 1 to 2 SD below normal or for patients with a history of fracture [99]. Calcium and vitamin D have been used for many years for the treatment of osteoporosis. A recent meta-analysis demonstrated a clinically and statistically significant prevention of bone loss from the lumbar spine and forearm with calcium and vitamin D in CS-treated patients [101]. Those authors recommended prophylactic therapy with calcium and vitamin D for all patients who are being started on CS [101]. This recommendation is most appropriate for patients with low dietary calcium intake (< 1.0–1.5 g/d) and without contraindications to supplemental calcium (*eg,* renal calculi) [99]. Patients with a history of fracture or baseline osteoporosis should be given bisphosphonates (*eg,* alendronate, risedronate) [102] because these agents are beneficial in treating and preventing CS-induced osteoporosis [99,103–105]. A recent meta-analysis including 13 trials and 842 patients taking at least 7.5 mg/d prednisone confirmed that bisphosphonates improve BMD [101]. The risk of spinal fractures was reduced 24%, although this was not statistically significant (OR: 0.76; 95% CI: 0.37, 1.53) [101]. Data regarding other potential therapies (*eg,* androgens, fluoride, intranasal calcitonin) are limited. The role of these agents in the treatment or prevention of CS-associated osteoporosis needs to be elucidated.

Peptic ulcer disease

The association of CS use and peptic ulcer disease (PUD) is controversial. CS were associated with an increased risk of PUD and gastrointestinal hemorrhage in some studies [106], but a meta-analysis failed to find an increased incidence of PUD among CS-treated patients compared with controls [107]. Given the conflicting data, the risk (if any) of PUD associated with CS appears to be small. In our series, only one of 41 patients (2.5%) treated with high-dose prednisone for 3 months developed a peptic ulcer [8••]. Because endoscopies were only performed for clinical indications, occult (asymptomatic) disease could have been missed. The benefit of histamine-2 antagonists or antacids to prevent PUD in CS-treated patients has not been established. However, patients with a history of PUD or receiving concomitant medications that increase the risk of PUD (*eg,* nonsteroidal antiinflammatory agents) may benefit from prophylaxis with histamine-2 antagonists or proton pump inhibitors. The use of prophylaxis in other low-risk populations needs to be individualized.

Miscellaneous complications of corticosteroids

As outlined in Table 2, CS have protean side effects, ranging from life-threatening opportunistic infections to cosmetic changes (*eg,* Cushingoid features). For some patient populations (*eg,* age > 70, significant obesity, diabetes mellitus, serious psychiatric disease), the risk of CS often exceeds the benefit. In such patients, we consider alternative therapeutic modalities. Among CS-treated patients, careful monitoring and patient education are essential to identify complications to modify dose or therapy at the earliest possible time.

Recent consensus statements and recommendations for therapy

Given the potential for debilitating side effects with CS therapy, recent editorials [108,109] and International Consensus Statements [3,10] argue that high-dose CS should be discouraged in IPF. Both consensus statements [3,10] advocate an individualized approach to treating IPF/UIP and acknowledge that not all patients should be treated. For patients requiring treatment, both societies recommend combining an immunosuppressive agent (AZA or cyclophosphamide) with prednisone or prednisolone (0.5 mg/kg/d for 4 weeks, with gradual taper) [3,10]. When contraindications to CS exist, either AZA or cyclophosphamide alone should be used. This is a substantial departure from earlier regimens advocating high-dose prednisone [20,23,110]. These recommendations are reasonable but have not been validated in scientific trials. However, we agree that the era of high-dose CS for prolonged periods has ended [109]. Given the paucity of data, firm recommendations regarding indications, dose, or duration of CS treatment for UIP cannot be given. We see no role for CS for patients with a chronic course, extensive fibrosis, and absence of GGO on HRCT or patients with specific contraindications. However, a trial of CS (with or without concomitant AZA or cyclophosphamide) is reasonable in patients with GGO on HRCT, a subacute or deteriorating course,

young age, and no contraindications to CS. In this context, a trial of prednisone (40 mg/d for 4–8 weeks, with a taper to 20 mg within 3–4 months) is reasonable. The dose and duration need to be individualized depending on the response and the presence or absence of side effects. Therapy with CS should be continued beyond 3 or 4 months only when patients exhibit unequivocal and objective responses to therapy. Subjective improvement is not adequate to justify continuing a therapy with potential cumulative toxicities.

Assessing response to therapy

Sequential physiologic studies are critical to assess the response to therapy [3,10,111,112]. Optimal parameters to follow the course of IPF have not been validated. We use serial spirometry (*eg*, forced vital capacity and forced expiratory volume in 1 second), 6-minute walk tests with oximetry, and DLCO to monitor response to therapy. Changes in forced vital capacity are usually adequate to track the course of the disease; DLCO is more sensitive but less reproducible. Six-minute walk tests with oximetry are noninvasive, relatively inexpensive, and invaluable in the initial assessment and longitudinal assessment of IPF/UIP [113]. The value of formal cardiopulmonary exercise testing is unproven. Criteria established by the American Thoracic Society to define physiologic improvement are reasonable (*ie*, $\geq$10% in total lung capacity or vital capacity, $\geq$15% increase in DLCO, $\geq$ 4% increase in O_2 saturation, or $\geq$ 4-mm increase in arterial oxygen pressure during exercise [3]. The role of serial HRCT in evaluating response to therapy has not been clarified.

Novel (future) agents

Unfortunately, current therapies for IPF based on altering the inflammatory component are marginally effective. The dictum *nollo nocere* is highly relevant, when potentially toxic drugs such as CS or immunosuppressive or cytotoxic agents are used for prolonged periods of time. Judicious and careful use of these drugs, with objective monitoring, is mandatory. Major advances in the treatment of IPF/UIP await the development of novel therapies that prevent fibroproliferation and/or enhance alveolar reepithelialization [58••]. Agents that have been tested in pilot studies include pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) [114], *N*-acetylcysteine [115], and interferon-γ [97]. Novel agents that inhibit fibrosis *in vitro* or in animal models and are worthy of study in future clinical trials include captopril [58••,116], platelet-activating factor receptor antagonists, inhibitors of leukocyte integrins, cytokines or proteases [88,117], keratinocyte growth factor [118,119], relaxin [120], and lovastatin [121].

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